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ENVIRONMENTAL TERATOGENS

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MECHANISMS

THE MECHANISMS OF teratogenesis fall into two broad categories based on the etiology of congenital malformations: errors in genetic programming based on deviations in the genotype of the embryo or the low probability for error of a normal genotype of the embryo or the low probability for error of a normal genotype, and environmental agents or factors that interact with an embryo during the period of development, such as drugs, chemicals, radiation, hyperthermia, infections, abnormal maternal metabolic states, or mechanical factors.

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The etiology of human malformations includes both genetic and environmental factors, as well as a large category labeled unknown (Table I).[1,2] Many geneticists believe that a significant proportion of congential malformations of unknown etiology are polygenic.[3,4] Thus, malformations with an increased recurrent risk, such as cleft palate, anencephaly, spina bifida, congenital heart disease, pyloric stenosis, talipes equinovarus, and congenital dislocation of the hip fit the criteria for polygenic inherited disease. These malformations also happen to fit the criteria for multifactorial disease.[3,5] Included in the unknown category are malformations that occur spontaneously at a very low frequency simply because there is a low probability that spontaneous errors of development will occur. Thus, particular genotypes have an inherent malformation rate based on the fact that embryonic development is a very complicated process and has a variable but low probability of going awry just as DNA duplication, for example, is not an error-free process. The explanation of the etiology and mechanisms of teratogenesis for this large group of malformations with unknown etiology will depend on identifying the genes involved in polygenic or plurogenic processes, interacting genetic and environmental determinants of multifactorial traits, and the mathematical risks for error during important embryonic processes of normal development. Until this triple identification can be accomplished, we will continue to label a large proportion of human malformations as having hypothetical etiologies.

The two etiologic categories of teratogenic agents, environmental and genetic, have different pathologic processes that result in embryopathology. Congenital malformations due to genetic etiology have a spectrum of pathologic processes that result from gene deficiency, gene abnormality, chromosome rearrangement, chromosome deletion, or chromosome excess, resulting in abnormal development. The pathologic nature of this process is determined before conception, or at least before differentiation, because of the presence of inherited or newly acquired genetic abnormalities. Although environmental factors may modify the development of the genetically abnormal embryo, the genetic abnormality is the predominant contributor to the pathologic process. (This review will not discuss the mechanisms involved in hereditary malformations, but rather will consider the mechanisms involved in malformations that are primarily environmentally produced.)

The basic tenets of environmentally produced malformations are that teratogens or teratogenic milieus have certain characteristics in common.

Stage sensitivity indicates that susceptibility to teratogenesis varies during gestation so that the three stages of development have the following associ-

TABLE I. ETIOLOGY OF HUMAN MALFORMATIONS OBSERVED DURING THE FIRST YEAR OF LIFE

Suspected cause	*Percent of total*
Genetic	
Autosomal genetic disease	15–20
Cytogenetic (chromosomal abnormalities)	5
Unknown	
Polygenic	65
Multifactorial (genetic-environmental interactions)	
Spontaneous error of development	
Synergistic interactions of teratogens	
Environmental	
Maternal conditions: Diabetes; endocrinopathies; nutritional deficiencies, starvation; drug and substance addictions	4
Maternal infections: Rubella, toxoplasmosis, syphilis, herpes, cytomegalic inclusion disease, varicella, Venezuelan equine encephalitis, parvovirus B19	3
Mechanical problems (deformations): Abnormal cord constrictions, disparity in uterine size and uterine contents	1–2
Chemicals, drugs, radiation, hyperthermia	<1
Preconception exposures (excluding mutagens and infectious agents)	

Adapted from Brent[1,2]

ated characteristics of teratogenesis: from fertilization through early postimplantation, the embryo has relatively few cells and a great capacity for replacement of omnipotent cells. Thus, the effect of an embryotoxic insult is typically an all-or-none phenomenon, because either the agent affects enough cells to kill the embryo or so few cells are affected that the embryo is able to repair itself effectively. This does not mean that there are no agents that cannot increase viable malformations but that the risk is much lower than during early organogenesis and that death of the embryo is the predominant pathologic event. The second stage, the period of organogenesis (from day 18 through about day 60 of gestation in the human), is the period of greatest sensitivity to teratogenic insults and the period when most gross anatomic malformations can be induced. Most major malformations cannot be developmentally produced after the 36th day of gestation except for the genitourinary system, palate, the brain, or deformations due to problems of constraint, disruption, or destruction. The third stage, the fetal period, is characterized by histogenesis involving cell growth differentiation and migration. Teratogenic agents may permanently or temporarily decrease cell populations by producing cell death, cell growth retardation, or inhibiting cell differentiation. There is, of course, some overlap, in that permanent cell depletion may be produced earlier than the 60th day.

Dose-response relationships refer to quantitative correlation of the magnitude of embryopathic effects to the dose of drugs and chemicals. This is extremely important when comparing effects in different species because mg/kg doses are frequently, at most, rough approximations. Dose equivalence between species can only be accomplished by pharmacokinetic studies and dose response curves in humans and in the species studied.

Threshold effects refer to the dosage or level of exposure below which the incidence of death, malformation, growth retardation, or functional deficit is not statistically greater than that of controls. This is usually from one to three orders of magnitude below the teratogenic or embryopathic dose for drugs and chemicals that kills or malforms half the embryos. Every teratogenic substance has an absolute no effect dose unless it can produce its effect in a single cell (stochastic phenomenon, Table II).

Genetic variability in mammals determines differences in placental transport, absorption, metabolism, and distribution of an agent, and accounts for some variations in teratogenic effects between species and individual subjects.

Infections are exceptions to some ot the basic tenets of teratogenesis because dose and time of exposure cannot be demonstrated for replicating teratogenic agents. Therefore, dose-response relationships, threshold effects, and genetic variability cannot be demonstrated in humans and in many experimental animal models.

Based on his review of the literature, Wilson[6,7] proposed possible mechanisms of teratogenesis: mutation, chromosomal aberrations, mitotic interference, altered nucleic acid synthesis and function, lack of precursors, substrates, or coenzymes for biosynthesis, altered energy sources, enzyme inhibition, osmolar imbalance, alterations in fluid pressures, viscosities, and osmotic pressures, and altered membrane characteristics. This list illustrates the many levels at which embryonic development is vulnerable to errors or disruptive influences. Unfortunately, this approach may generate some confusion when one attempts to determine etiology for two reasons: the pathologic processes could result from genetic or environmental factors, and that an environmental agent can induce one of these pathologic processes does not guarantee that exposure will result in teratogenesis. Thus, while the mechanisms proposed by Wilson provide a format of theoretical teratogenic mechanisms, it does not relate these to known teratogens nor does it enable us to predict teratogenesis in humans if an agent exhibits one of these characteristics in an experimental test system. We propose a list of mechanisms in Table II for our discussion of known teratogenic agents in the human.

TABLE II. RELATION OF DISEASES PRODUCED BY ENVIRONMENTAL AGENTS AND THE RISK OF OCCURRENCE

Relationship	*Pathology*	*Site*	*Diseases*	*Risk*	*Definition*
Stochastic phenomena	Damage to a single cell may result in disease	DNA	Cancer, mutagen	Exists at all exposures, although at low exposure the risk is below the spontaneous risk	The incidence of disease increases with exposure but the severity and the nature of the disease in the patient remain the same
Threshold phenomena	Multicellular injury	Great variation in etiology affecting many cell and organ processes	Malformation, death, growth retardation, chemical toxicity, etc.	Completely disappears below a certain threshold dose	Both the severity and incidence of disease increase with higher exposures

From Brent[297]

The mechanisms proposed by Wilson describe effects that may be attributable to an agent under defined experimental conditions. It is, however, improbable that a drug, chemical, or other agent will have only one effect on a biologic system. It is also improbable, even if one assumes that the mechanisms of action of a particular agent may be known, that in utero exposure to that agent will result in congenital malformations without taking into consideration developmental state or dose. Rather than to select possible mechanisms of action from a list to test which action fits the agent, a more practical approach is to study the effects of the agents in question to determine their mechanisms of action.

Before we discuss environmental agents for which the usual or attainable exposure has been shown to pose a teratogenic risk for humans, we shall discuss briefly the controversial topic of the teratogenic risk of unidentified or suspected environmental agents.

BASELINE RISK OF HUMAN DEVELOPMENT

Human development is not without some risk of fetal death or abnormal development: it is estimated that as many as 50% of all fertilized ova are lost within the first three weeks of development[8] and the World Health Organization[9] estimated that 15% of all clinically recognizable pregnancies end in spontaneous abortions. This means that, as a conservative estimate, 1,150 clinically recognized pregnancies will result in approximately 150 miscarriages and that 30 to 60 infants among the remaining 1,000 live births will have congenital anomalies. The true incidence of pregnancy loss is much higher, but undocumented pregnancies are not included in the conservative risk estimate. (Estimates of fetal loss during gestation and the last gestational day in which selected malformations may be induced are presented in Table III.) The 3 to 6% incidence of malformed offspring is the background risk for human maldevelopment. Partly because the etiology of approximately 65% of spontaneous malformations is unknown, there is considerable debate concerning the contribution of unidentified environmental agents to the causation of malformations of unknown etiology. It is very difficult to make a reliable estimate of this hazard because the large number of pharmaceutical, industrial, and agricultural chemicals increases the probability of exposures involving multiple agents, and the threshold susceptibility of individual subjects varies because of human genetic heterogeneity.

Because of the anxiety created by the uncertainty of risk estimates for the human, however, it is of utmost importance to evaluate reported associations crtically: "Let us be on the alert by all means and report our observations, but we must be critical, because many pregnant women and their husbands are unnecessarily upset by uncritical accusations of drugs as being the cause of all

TABLE III. MECHANISMS OF TERATOGENESIS

Cell death beyond recuperative capacity of the embryo/fetus
Mitotic delay: increase in the length of the cell cycle
Retarded differentiation: slowing or cessation in the process of differentiation
Physical constraint and vascular insufficiency
Interference with histogenesis by processes such as cell depletion, necrosis, calcification, or scarring
Inhibited cell migration and cell communication

From Beckman and Brent[298]

congenital abnormalities.''[10] Uncritical reviews of data relating to humans or attempting to extrapolate animal data directly to humans without human confirmation do not aid the health care community in estimating the hazard that exposures to specific agents present to a human fetus. Unfortunately, uncritical evaluation of reports suggesting causal associations between suspected agents and human malformations can lead to misinformation, such as the erroneous association of Bendectin® with congenital defects.

The safety of Bendectin,® a preparation containing doxylamine succinate, pyridoxine hydrochloride, and, until 1977, dicyclomine hydrochloride, has been a matter of controversy in the media and the courts. Rothman et al.[11] reported an association between Bendectin® and congenital heart disease, which was criticized on the basis of inadequate controls, primarily differential recall bias. That is, mothers of infants with congenital heart defects might recall the use of drugs, Bendectin® in this case, more frequently than the mothers of healthy infants. In a second effort to elucidate an association between congenital heart defects and the use of several drug preparations during pregnancy, Zierler and Rothman[12] found no association (prevalence:odds ratio, 1:1) between Bendectin® and heart defects. Although their analyses could suggest only crude associations, the evidence was against Bendectin® as a cardiac teratogen. The subject has been reviewed and discussed by many.[13,14,15] The topic of misinformation and the inappropriate usage of data has been discussed recently by Wilson.[16]

It should be noted that most human teratogens have been identified by alert physicians or scientists. Epidemiologic studies, on the other hand, have been most helpful in understanding the frequency, trends, and incidence of congenital malformations. Although animal studies have been useful primarily in understanding the mechanism of action of known human teratogens, they also support epidemiologic studies by the development of animal models.[17] Even with complete pharmacokinetic studies in the human and animal spe-

cies, an animal model cannot be extrapolated with certainty to the human condition, an issue discussed thoroughly elsewhere.[17-20]

What is known concerning the mechanism of action of agents documented to cause congenital malformations in man or agents of particular current interest is discussed below. The American College of Obstetricians and Gynecologists has recently published a bulletin summarizing selected human teratogens and their effects.[21]

HUMAN TERATOGENIC AGENTS

Alcohol. Jones et al.[22-24] described the fetal alcohol syndrome in children with intrauterine growth retardation, microcephaly, maxillary hypoplasia, and reduction in the width of palpebral fissures. Cardiac abnormalities also were seen. Approximately one third of the children of alcoholic mothers had fetal alcohol syndrome,[22,23] and all affected children evidenced developmental delay.[24]

A period of greatest susceptibility and a dose-response relationship have not yet been established.[25] Although we are reluctant to claim that malformations are due to single exposures to alcohol in humans, binge drinking early in pregnancy has been suggested to be associated with neural tube defects, and seasonal variation in the incidence of neural tube defects has been associated with concomitant seasonal variations in alcoholism.[26] Although chronic consumption of 6 oz of alcohol per day constitutes a high risk, fetal alcohol syndrome is not likely when the mother drinks fewer than two drinks (equivalent to 2 oz of alcohol) per day.[27] Larsson et al.[28] evaluated children exposed to varying amounts of alcohol in utero and concluded that reduction of alcohol consumption at any time in pregnancy reduced the severity of the fetal alcohol syndrome but did not significantly reduce the risk of some degree of physical or behavioral impairment. The human syndrome is likely to involve the direct effects of alcohol and its metabolite, acetaldehyde,[29] and the indirect effects of genetic predisposition and poor nutrition. Alcoholism also is associated with smoking and the use of other drugs.

Sulik and Johnston[30] have reported an animal model exhibiting craniofacial features in mice similar to those characteristic of fetal alcohol syndrome in humans. Chernoff[31] showed that the incidence of congential defects and the maternal alcohol level were inversely related to maternal alcohol dehydrogenase levels in three mouse strains. It has been suggested that inhibition of cell growth is the primary effect of alcohol, resulting in developmental abnormalities.[32] Direct effects of ethanol and acetaldehyde on the development of mouse embryos cultured during the period of organogenesis demon-

TABLE IV. ESTIMATED OUTCOME OF 100 PREGNANCIES VERSUS TIME FROM CONCEPTION

	No. live births during interval	*Percent survival to term**	*Percent death during interval*	*Last time for induction of selected malformations†*
Preimplantation				
0–6 days	0	25	54.55	
Postimplantation				
7–13 days	0	55	24.66	
14–20	0	73	8.18	
3–5 weeks	0	79.5	7.56	23 day cyclopia; sirenomelia 26 day anencephaly 28 day meningomyelocele 34 day transposition of great vessels
6–9	0	96.00	6.52	36 day cleft lip, limb reduction
defects				6 wk diaphragmatic hernia; rectal atresia, ventricular septal defect, syndactyly 9 wk cleft palate
10–13	0	92.00	4.42	10 wk omphalocele 12 wk hypospadias
14–17	0	96.26	1.33	
18–21	0.01	97.56	0.85	
22–25	0.04	98.39	0.31	
26–29	0.24	98.69	0.30	
30–33	0.66	98.98	0.30	
34–37	9.72	99.26	0.34	
38+	14.33	99.32	0.68	38+ wk CNS cell depletion

*An estimated 50 to 70% of all human conceptions are lost in the first 30 weeks of gestation[8] and 78% are lost before term. From Robert and Lowe[286]

†Modified from Schardein[120]

Data from Kline and Stein[287]

strated that the exposures have similar effects but that the acetaldehyde was 10,000 times more embryotoxic than ethanol and that their mechanisms of action are likely to be very different.[33] Recent studies also suggest an indirect effect in rats: placental transport of amino acids to the fetus is decreased at levels of alcohol that do not effect fetal development.[34]

Antineoplastic drugs. Antineoplastic drugs are discussed briefly as a class because of reported developmental effects from occupational exposures. Drugs known to be teratogenic in the human will be discussed in depth.

Antineoplastic drugs inhibit cell growth or kill rapidly growing cells, and because they are often administered in the range of maximum tolerated dosages, teratogenic risk may be high at therapeutic doses for exposed embryos of pregnant patients. Therapeutic exposures do not necessarily increase teratogenic risk, however, because appropriate single- or multiple-drug regimens may be designed that lower the risk.[35] Also, even considering drugs that definitely increase teratogenic risks, no antineoplastic drug has been shown to be 100% teratogenic even at therapeutic doses, and many have not been associated with increased risk of congental malformations. It should be noted that some of these agents present minimum risk, and no known agent presents a teratogenic risk of 100%.

The occupational risk for hospital personnel exposed through inhalation or skin absorption has not been determined. Major problems in defining teratogenic risk in this population are: the class of antineoplastic drugs is composed of several chemically unrelated drugs (e.g., alkylating agents, antimetabolites, antibiotics, spindle poisons, and hormones) that have different mechanisms of action, pharmacokinetics, and side effects; the level of exposure is difficult to define; and the nursing occupation is associated with increased reproductive risk.[36] As a general rule, at doses somewhat below the severely cytotoxic dose of chemotherapeutic agents that have teratogenic potential, one would not expect a teratogenic risk.

Reported embryotoxic effects in pregnant hospital personnel resulting from antineoplastic drugs as a class[37] certainly indicate that all precautions should be taken to protect personnel at risk. Rather than assume that all antineoplastic drugs present an equal and great risk, however, efforts should be made to identify the drug(s) and levels of exposure that pose serious threats. Because some exposure to antineoplastic drugs most likely cannot be avoided, this information is necessary to reduce both the actual risk to personnel and the anxiety concerning their perceived risk.

Aminopterin and methotrexate. Aminopterin-induced therapeutic abortions have been shown to result in malformations (hydrocephalus, cleft palate, meningomyelocele) in some abortuses.[38,39] Three case reports of

children receiving in utero exposure to aminopterin observed growth retardation, abnormal cranial ossification, high-arched palate, and reduction in derivatives of the first branchial arch.[40-42]

Methotrexate (methylaminopterin) ingestion during the first two months[43] or for five days between the eighth and tenth weeks[44] resulted in the absence of digits.

Both compounds are folic acid antagonists that inhibit dihydrofolate reductase, resulting in cell death during the S phase of the cell cycle.[45] The clinical literature has been reviewed by Warkany.[46]

Dyban et al.[47] have reported abnormalities of cell proliferation and cytotoxicity employing rat blastomere cultures exposed to different doses of aminopterin. Although methotrexate was not teratogenic in monkeys,[48] Skalko and Gold[49] demonstrated a threshold effect and a dose-dependent increase in malformations in mice.

Androgens. Masculinization of female external genitalia has been reported following in utero exposure to large doses of testosterone.[50] methyltestosterone,[51] and testosterone enanthate.[52] The masculinization is characterized by clitoromegaly with or without fusion of the labia minora.

As an illustration that androgens can affect only tissues with androgen receptors, inherited male pseudohermaphroditism is a syndrome in which the testes secrete normal amounts of testosterone but receptor binding in target tissues is defective. The result is that genotypic males undergo feminine development.[53] This is the same result that a lack of androgens has on the development of sex structures in the male.[54] Thus, it can be seen that either an excess or a deficiency in androgens can affect only those tissues with androgen receptors.

Many animal models demonstrate the masculinizing effects of androgens. Well-known studies were performed by Greene et al.[55] in rats, Raynaud[56] in mice, Bruner and Witschi[57] in hamsters, Jost[58] in rabbits, and Wells and Van Wegenen[59] in monkeys. These studies demonstrated masculinization of the urogenital sinus, its derivatives, and external genitalia, although there was little effect on the mullerian ducts and ovarian inversion did not occur. Based on experimental animal studies, any effects of prenatal exposure to androgens on behavioral masculization will be rare because the androgen must be aromatizable to an estrogen to affect sexual differentiation of the brain,[60] and estrogen receptors in the brain have not been identified before birth in the mouse, rat, or monkey.[60,61]

Coumarin derivatives. Nasal hypoplasia following exposure to several drugs, including warfarin, during pregnancy was reported by DiSaia.[62] Kerber et al.[63] were the first to suggest warfarin as the teratogenic agent. Cou-

marin anticoagulants have since been associated with nasal hypoplasia, calcific stippling of secondary epiphyses, and central nervous system abnormalities.[64-67] Barr and Burdi[68] described warfarin embryopathy and Warkany, besides summarizing the clinical data, provides an excellent overview of the difficulties in relating a congenital malformation to an environmental cause.[69-70] There is an estimated 10–25% risk for affected infants following exposure during the period from the eighth through the 14th week of pregnancy, although this risk has been reported to be much lower in some series, and factors other than dose and gestational stage seem to play a role.

Coumarin has been shown to inhibit the formation of carboxyglutamyl residues from glutamyl residues, decreasing the ability of proteins to bind calcium.[71] Inhibition of calcium binding by proteins during embryonic/fetal development, especially during a critical period of ossification, could explain the nasal hypoplasia, stippled calcification, and skeletal abnormalities of warfarin embryopathy.[66] Microscopic bleeding does not seem to be responsible for these problems early in development.[68]

A recent case report was unique in that the time of exposure to warfarin was between eight and 12 weeks of gestation, and the infant presented Dandy-Walker malformation, eye defects, and agenesis of the corpus callosum.[72] Although this case report represents the clearest evidence for a direct effect of warfarin on the developing central nervous system rather than an effect mediated by hemorrhage, it is the only report with the exposure so well defined and occurring before the appearance of vitamin K-dependent clotting factors. A useful animal model for warfarin embryopathy has not yet been reported.

Cyclophosphamide. Cyclophosphamide is a widely used antineoplastic agent that increases the teratogenic risk in the human, but the magnitude of the risk is as yet undefined. Defects include growth retardation, ectrodactyly, syndactyly, cardiovascular anomalies, and other minor anomalies.[73,74] Ten normal pregnancies have been reported following cyclophosphamide exposure.[35]

Experimental animal studies in rats,[75,76] mice,[77] rabbits,[78] and monkeys[79] have shown distinct developmental stage specificity, dose-effect relationships, and a high sensitivity of nervous system and mesenchymal tissues.[80]

The current knowledge of the mechanism of cyclophosphamide teratogenesis has been reviewed recently: cytochrome P450 monooxygenases convert cyclophosphamide to 4-hydroxycyclophosphamide, which in turn breaks down to phosphoramide mustard and acrolein.[80] Phosphoramide mustard and acrolein are thought to produce the teratogenic effects associated

with exposures to cyclophosphamide by interacting with cellular DNA in an as yet undefined manner and resulting in cell death. Tissue sensitivity to phosphoramide mustard and acrolein is thought to be related to such processes as detoxification and cellular repair.

Diethylstilbestrol. The first abnormality reported following exposure to diethylstilbestrol during the first trimester was clitoromegaly in female newborns.[81] Much later, Herbst et al.[82,83] and Greenwald et al.[84] reported an association of vaginal adenocarcinoma in female offspring following first-trimester exposures. Further studies revealed that almost all of the cancers occurred after 14 years of age and only in those exposed before the 18th week of gestation.[85,86] There is a 75% risk for vaginal adenosis for exposures before the ninth week of pregnancy, but the risk of adenocarcinoma is extremely low, 1:10,000.[87]

Although there does not appear to be an adverse effect on the rate of conception,[88] it is not clear whether the anatomic abnormalities of the uterus and cervix induced by intrauterine exposure to diethylstilbestrol increase the probability of such reproductive problems as spontaneous abortions.[89,90]

There have been reports that males exposed to diethylstilbestrol in utero had genital lesions and abnormal spermatozoa, but no malignancies were observed.[91] A more recent epidemiologic study by Leary et al.[92] reported no increase in the male risk for genitourinary abnormalities, infertility, or testicular cancer. The controversial nature of the effects of diethylstilbestrol exposure on males may be attributable to study design or, more likely, to the fact that dose levels have varied greatly according to different regimens. A review of the syndrome has been presented by Ulfelder.[93]

Diethylstilbestrol is a potent nonsteroidal estrogen and, as in the case of steroidal estrogens, must interact with receptor proteins present only in estrogen-responsive tissues before exerting its effects by stimulting RNA, protein, and DNA synthesis. Its alleged carcinogenic effect is most likely indirect: exposure results in the presence of columnar epithelium in the vagina, and this "misplaced tissue" may have a greater susceptibility to developing adenocarcinoma, such as teratomas, and other misplaced tissues are more susceptible to malignant transformation.

Teratogenic and transplacental carcinogenic effects following in utero exposure to diethylstilbestrol have been demonstrated in rats,[94,95] mice,[4,96] and hamsters[84] A major difficulty in studies of its mechanism of action is the extensive biotransformation that occurs in the adult mammal, reviewed by Metzler.[97] These transformations recently have been demonstrated in the hamster fetus.[98]

Diphenylhydantoin. Chronic exposure to diphenylhydantoin has been suggested to present a maximum of 10% risk for the full syndrome and a maximum of 30% risk for some anomalies.[99-102] Although cleft lip and palate, congenital heart disease, and microcephaly have been reported, hypoplasias of the nails and distal phalanges are possibly more specific malformations in exposed fetuses.[64,103] Hanson et al.[104] noted that, although the hydantoin syndrome is observed in 11% of the subjects in their study, three times as many have mental deficits. The hydantoin syndrome has been reviewed by Hanson and colleagues.[104] It should be mentioned that prospective studies demonstrate a much lower frequency of effects, and some demonstrate no effect; thus, the overall prospective risk may be much lower for the classically reported effects.

Factors associated with epilepsy may contribute to the etiology of these malformations: based on the United States Collabotative Perinatal Project and a large Finnish registry, the incidence of malformations was 10.5% when the mother was epileptic, 8.3% when the father was epileptic, and 6.4% when neither parent was affected.[41]

Cleft lip and palate as well as limb defects have been produced in rabbits[105] and in mice,[106,107] and the malformation rate was dose dependent.[108] Cleft palate in mice caused by diphenylhydantoin could not be prevented by giving up to 100 mg of folic acid per kg of body weight.

Diphenylhydantoin exerts a stabilizing effect on cell membranes by affecting ion movements. There also may be some effect on folate and vitamin K metabolism.[109]

Herbicides: Agent Orange. The effects of herbicides, particularly Agent Orange, on human reproduction, are the subject of much current debate. Agent Orange is composed of the herbicide, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). 2,4,5-T in turn, is contaminated by traces of 2,3,7,8-tetrachlorobenzo-p-dioxin (dioxin). The contamination of 2,4,5-T with dioxin has varied over the last several decades with a trend toward decreasing its dioxin content. Aerial spraying in New Zealand with 2,4,5-T has been reported to be associated with an increase in the incidence of talipes but not of any defect of the central nervous system.[110] No epidemiologic studies support a causal relationship between 2,4,5-T and human malformations.

The debate concerning dioxin involves both direct effects on the fetus following exposure of pregnant women to industrial accidents (Seveso, Italy, 1976[111]) or the effects on human development following exposure of men in Vietnam, primarily Vietnamese, American, and Australian soldiers. A recent compilation of the literature involving exposures during the Vietnam

conflict is particulary interesting because it presents data from Vietnamese sources.[112] Unfortunately, there are deficiencies in the epidemiologic methods used by the Vietnamese, as there are in similar studies conducted in the United States and Australia. Methodologic deficiencies have been discussed by others.[113-116] Despite the known toxicity of dioxin, evaluation of the data suggests that human development has not been affected, but this may be because teratogenic exposures are not likely to be attainable in the human as with the experimental exposure of animals and although dioxin is teratogenic at low doses the maternally toxic and embryotoxic doses are quite similar in contrast to other classical teratogens.

Lithium carbonate. Lithium carbonate, a widely used antidepressant since 1947, was first associated with human congenital malformations in 1970.[117,118] The International Register of Lithium Babies, maintained by Dr. Morton Weinstein, listed 25 malformed infants out of 225 cases by 1983.[119] Malformations described include heart and large vessel anomalies, Epstein's anomaly, neural tube defects, talipes, microtia, and thyroid abnormalities.[120] Lithium carbonate appears to be a human teratogen at therapeutic dosages. Although shown to induce malformations in approximately 10% of exposed fetuses, critical parameters of exposure that would allow a more accurate estimation of the teratogenic risk of lithium carbonate have not yet been elucidated. Because of the importance of this therapy, it is difficult to decide on the appropriate course of action during pregnancy.

Rodents are the only laboratory animals shown to be sensitive to the teratogenic effects of lithium salts. Lithium carbonate induces cleft palate in mice.[121] Lithium chloride produced cleft palate and abnormalities of the eyes and external ears in rats,[122] but these findings were not replicated with similar exposures using a different strain of rat.[123] The lack of a good animal model for congenital heart disease has hampered the study of the mechanism of lithium teratogenesis.

Methylmercury. There have been several incidences of human exposures to methylmercury as an environmental pollutant or as a fungicide present on seed grain consumed by humans. In Minamata, Japan, the local population was exposed by ingesting fish caught in a bay heavily polluted by methylmercury. In 1953 neurologic abnormalities began to develop in the population, and approximately 38% of the afflicted people died. About 6% of children born between 1955 and 1959 were affected: cerebral palsy and associated microcephaly were common features, with few other congenital defects.[124,125] Snyder[126] described the severe damage to the central nervous system in the offspring after ingestion by the mother of meat from a pig fed

seed grain containing a mercurial fungicide. Seed grain containing a methylmercury fungicide was responsible for fetal exposures in Iraq, when pregnant women consumed bread inadvertently prepared using the seed grain.[127,128] Cerebral palsy, as well as motor and mental impairments, were reported. Harada[129] has reviewed all the clinical aspects of congenital Minamata disease.

In vitro studies have shown that methylmercury in human blood is associated with erythrocytes and protein components, primarily lipoproteins.[130] The nature of this association and the biochemical basis of the biologic effects of organic mercury was attributed to interactions between methylmercury and -SH or -SS groups of proteins.[131]

Murakami[125] has reviewed experimental animal studies. Methylmercury exposures have been associated with an increased incidence of cleft palate and central nervous system abnormalities.[132-134] Organic mercury has been reported to concentrate preferentially in the fetal brain.[109,135] No deleterious effects were observed in rats after chronic low doses of methylmercury hydroxide.[136]

Oxazolidine-2,4-diones (trimethadione, paramethadione). Trimethadione and paramethadione are antiepiliptic oxazolidine-2, 4-diones that distribute uniformly throughout body tissues and exert their effects by means of the action of their metabolites. These drugs affect cell membrane permeability and vitamin K-dependent clotting factors, but their primary mode of action is unknown.

Zackai et al.[137] described a fetal trimethadione syndrome characterized by developmental delay, V-shaped eyebrows, low-set ears with anteriorly folded helix, high arched palate and irregular teeth. German et al.[138] reported similar findings plus cardiac anomalies. Feldman et al.[139] and Goldman and Yaffe[140] have reviewed the clinical findings in the literature and from their own observations. There are wide variations in reported risk, with estimates as high as 80% for major or minor defects. Because the number of exposures is small, actual risk could vary considerably from these figures. It is unlikely that we will ever be able to ascertain the risk accurately, since the drug should not be used in pregnant women.

Mice exposed to high doses of trimethadione on days eight to 10 or 11 to 13 of gestation had a high incidence of fetal growth retardation and abnormalities of the viscera and skeleton; especially common were aortic arch and vertebral defects.[141]

Polychlorinated biphenyls. "Yusho" is the English term for the polychlorinated biphenyl (PCB) poisoning first identified in Japan in 1968[142] and

later in Taiwan in 1979.[143] PCBs consumed in contaminated cooking oil by pregnant women resulted in fetal yusho or a fetal PCB syndrome characterized by pigmented children (cola-colored) with characteristic low birth weights; pigmentation of the gums, nails, and groin; hypoplastic deformed nails; conjunctivitis with enlargement of the sebaceus glands of the eyelid; abnormal calcification of the skull; rocker bottom heel; and, possibly, an alteration in calcium metabolism.[109,143] The developmental effects of PCBs on the human have been reviewed recently.[109,143]

An important observation is the occurrence of congenital yusho in children conceived after use of the contaminated oil was discontinued; residual contaminants in the bodies of pregnant women resulted in congenital yusho in 13 children born up to two years after the last ingestion of the contaminated oil, and slight brown staining of the skin continued for approximately four years (Harada, as reported by Miller[144]). As pointed out by Miller,[144] not one of the reports of congenital yusho is comprehensive. The incidence generally is not well documented and follow-up studies are lacking, so that the total risk of an exposed population is almost impossible to assess at this time.

Several circumstances have inhibited a full evaluation of PCB teratogenicity in the human: technical difficulties in measuring PCB concentrations; although dose-response relationships have been demonstrated for the toxic effects, there are no dose-response data for human developmental effects; and PCB-contaminated cooking oil contained several PCB isomers as well as toxic polychlorinated quarterphenyls and polychlorinated dibenzofurans.

Administration of Kanechlor (one of the PCBs present in the contaminated cooking oil) to pregnant rats resulted in maternal and fetal toxicity at the highest doses used and fetal growth retardation at lower doses.[145] Although the incidence of malformations was not increased, studies suggested a decrease in maze-learning speed of the rats.[146] Kunita et al.[147] employed nonpregnant rats and monkeys to study the hepatic hypertrophy, immunosuppression, hepatic microsomal enzyme activation, and dermal symptoms resulting from exposures to various combinations of PCBs, polychlorinated quarterphenyls and dibenzofurans. Although Kunita et al.[147] concluded that polychlorinated dibenzofurans are the primary agent causing yusho in rats, there is great variation in the effects of different polychlorinated aromatics in different species.

Occupational exposure to PCBs, which may occur during repair or in accidents involving PCB-containing transformers and capacitors, can result in exposures 10 to 1,000 times above those in nonoccupationally exposed

individuals.[148] Because of the qualitative nature of PCB identification and measurements currently used for human exposures,[148] it is difficult to estimate the teratogenic risk of occupational exposures to PCBs. It does appear, however, that most acute accidental occupational exposures present less teratogenic risk than do the chronic exposures that resulted in yusho.

It should be noted that the embryotoxic effects of PCBs reported in Japan occurred after ingestion of contaminated cooking oil, and that exposures from transformer oil-contaminated roads, fields, and livestock expose women to doses several orders of magnitude lower than those that occurred in Japan.

Progestins (female sex hormones). For the purpose of discussion, expediency justifies grouping together many compounds by generically using the term "sex hormones." Similarly, there are common references to "progestogens" or "progestational agents." This expediency is unfortunate when it occurs in epidemiologic studies, which do not list the composition of sex hormone exposures.[149-151] It also is often overlooked that, although various progestogens act by means of similar receptors, their potential androgenic effects can differ markedly. This point is critical to the appreciation of the virilizing effects of these compounds in humans. It has been shown, for example, that the pharmacokinetic parameters that estimate steroid bioavailability and metabolism show great variability among subjects and between steroids conveniently grouped together, such as "progestins."[152] One must assume that these differences in bioavailability and metabolism reflect differences in the biologic activity of these steroids in humans.

In contrast to progesterone and 17-alpha-hydroxyprogesterone caproate, high doses of some of the synthetic progestins have been reported to have virilizing effects in humans. Exposure during the first trimester to large doses of 17-alpha-ethinyltestosterone has been associated with masculinization of the external genitalia of female fetuses.[153,154] Similar associations result from exposure to large doses of 17-alpha-ethinyl-19-nortestosterone (norethadrone)[155] and 17-alpha-ethinyl-17-OH-5(10)estren-3-one (Enovid®).[156] The synthetic progestins, like progesterone, can influence only those tissues with appropriate steroid receptor proteins. Preparations with androgenic properties may cause abnormalities in the genital development of females only if present in sufficient amounts during critical periods of development.[153,155,157] In 1959 Grumback et al.[156] pointed out that labioscrotal fusion could be produced with large doses if the fetuses were exposed before the 13th week of pregnancy, whereas clitoromegaly could be produced after this period, illustrating that a specific maldevelopment can be induced only when susceptible embryonic tissues are in a restricted stage of development.

The World Health Organization recently has reported a suspicion that combined oral contraceptives or progestogens may be weakly teratogenic but that the magnitude of the relative risk is small.[158] In a large retrospective study, Heinonen et al.[149] reported a positive association between cardiovascular defects and in utero exposure to female sex hormones. A revaluation of some of the base data by Wiseman and Dodds-Smith,[159] however, did not not support the reported association. Another retrospective study conducted by Ferencz et al.[160] find no positive association between female sex hormone therapy and congenital heart defects. Although neither study disproved the positive association reported by Heinonen et al.,[149] their findings made the association less likely.

Epidemiologic studies have reported an association between exposures to female sex hormones, hormone pregnancy tests, oral contraceptives or progestogens, and congenital neural tube defects[161,162] and limb defects.[150,151] Further studies and revaluations have supported neither of these associations.[163-166] Recent reviews have discussed the evidence against the involvement of female sex hormones in nongenital teratogenesis.[6,167,168]

Further support for the absence of a nongenital effect of progestins comes from a recent report of a negative correlation between sex hormone usage during pregnancy and malformations,[169] no increased incidence in malformations following progesterone therapy to maintain pregnancy,[170] and no increased incidence in malformations following first trimester exposure to progestogens (mostly medroxyprogesterone) administered to pregnant women who had signs of bleeding.[171]

It is generally accepted that the actions of steroid hormones are mediated by specific steroid receptors,[172,173] and therefore only those tissues with the specific receptors can be affected by steroid hormones. It has been shown that 17-alpha-hydroxyprogesterone caproate (Delalutin®) does not cause developmental abnormalities in nonreproductive organs of mice.[174] Nonreproductive tissues of fetal primates are similarly unaffected by exposure to sex steroids because, for example, the nonreproductive tissues of fetal monkeys do not possess estrogen or progesterone receptors during early organogenesis.[61]

Radiation. The classic effects of radiation are cell death or mitotic delay. These effects are due to direct damage to cell chromatin and are expressed in offspring as gross malformations, intrauterine growth retardation, or embryonic death, each with a dose-response relationship and a threshold exposure below which no difference between an exposed and unexposed control population can be demonstrated.[175] Offspring born to patients receiving radiation therapy for various conditions exhibited growth retardation, eye malforma-

tions, and central nervous system defects.[176-178] Microcephaly is probably the most common manifestation following in utero exposure to high levels of radiation in humans.[179] Fetal exposure to radiation at Hiroshima resulted in microcephaly, growth retardation, and mental retardation.[180-182] In a recent review of radiation teratogenesis, Brent[175] pointed out that no malformation of the limb, viscera, or other tissue has been observed unless the child also exhibits intrauterine growth retardation, microcephaly, and/or eye malformations. The risk of major malformations is not increased by in utero exposure of 5 rads or less.[175]

Experimental animal models have shown that radiation-induced effects on the developing organism result from the direct action of ionizing radiation on the embryo and are not due to maternal effect.[175] Prior to implantation, the mammalian embryo is insensitive to the teratogenic and growth retarding effects of radiation and sensitive to the lethal effects.[183-185] Organogenesis is a stage sensitive to the teratogenic, growth-retarding, and lethal effects, but the embryo has some recuperative capacity.[184,186-188] Sensitivity to the teratogenic effects of radiation decreased during the fetal stage, but the fetus may still sustain permanent cell depletion since its recuperative capacity is less.[175] Permanent growth retardation is thus more severe following midgestation radiation. Because of its extended periods of organogenesis and histogenesis, the central nervous system retains the greatest sensitivity of all organ systems to the detrimental effects of radiation through the later fetal stages. Documented effects of prenatal exposure to ionizing radiation, which leads to brain malformation in experimental animals, are cell death and inhibition of cell migration.[189]

Substance abuse: street drugs. The contribution of street drugs (narcotics, marijuana, benzodiazepines, barbiturates, amphetamines, toluene) to the incidence of congenital malformations is difficult to assess, particularly because street drugs are of variable potency and purity, abusers neglect health care and nutrition, the frequency of multiple drug use is high, and there is a high incidence of infections and venereal disease among drug abusers.[190]

The most common effect of fetal exposure to narcotics (heroin, methadone, opiates, cocaine, and pentazocine) is that of intrauterine growth retardation not related to nutrition and premature birth.[190] No increased risk of congenital malformations has been substantiated. Cocaine abuse during pregnancy has been associated with an increased risk of spontaneous abortion and a detrimental effect on neurologic function and a low risk for urinary tract malformations.[191,294-296]

Data concerning marijuana (and hallucinogens in general),[192] amphetamines,[193] and barbiturates[190] are very unclear as to specific effects on the fetus because of multiple drug use, but no data support direct teratogenic effects in humans.

Diazepam has been associated with cleft lip with or without cleft palate,[194,195] but the association is not likely causal.

Although occupational exposure to toluene has not been shown conclusively to cause congenital malformations, there are case reports of malformations resulting from recreational abuse of toluene. Three case reports of abuse throughout pregnancy described microcephaly, central nervous system defects, minor craniofacial and limb abnormalities, and variable growth retardation.[196]

In summary, although cocaine abuse is associated with a low risk for certain malformation, there does not appear to be a significant increase in teratogenic risk associated with the abuse of narcotics, marijuana, benzodiazepines, barbiturates, amphetamines, or toluene, but there is an increase in fetal wastage, intrauterine growth retardation, and complications of pregnancy associated with street drug abuse.

Tetracycline. Antimicrobial tetracyclines inhibit bacterial protein synthesis by preventing access of aminoacyl transfer RNA (tRNA) to the messenger RNA (mRNA)-ribosome complex.[197]

Although tetracycline discolors teeth,[198] very high doses may depress skeletal bone growth and result in hypoplasia of tooth enamel.[199] No congenital malformations of any other organ system have been associated with antenatal tetracycline exposures. Several case reports of limb reduction defects in human embryos exposed to tetracycline are not supported by epidemiologic studies or animal studies. Tetracyclines complex with calcium and the organic matrix of newly forming bone without altering the crystalline structure of hydroxyapatite.[199] Although stunting has been produced in rats,[200] other experimental animal studies have found either no teratogenic effect[201] or ambiguous effects.[202]

Thalidomide. Lenz and Knapp[203,204] and McBride[205] were the first to describe thalidomide-induced phocomelia. Limb defects resulted from exposure limited to a two-week period from the 22nd to the 36th days of gestation: exposures from the 27th to the 30th days most often affect only the arm, whereas exposures from the 30th to the 33rd days resulted in both leg and arm abnormalities.[206] Although there was no association of mental retardation, brain malformations, or cleft palate, other abnormalities included facial

hemangioma, microtia, esophageal or duodenal atresia, deafness, and anomalies of the kidneys, heart, and external ears.[204,206,207] A high proportion of the fetuses exposed during the critical period were affected.

McCredie and McBride[208] suggested that the limb reduction defects exhibited a segmental pattern. McCredie[209] proposed that the segmental pattern was determined by peripheral nerves derived from the neural crest. McBride[210,211] and Stokes et al.[212] presented experimental evidence supporting an alternative proposal that the quantity of nerves was important: damage to peripheral sensory nerves results in preaxial abnormalities, and greater damage results in amelia.

Stephens and McNulty[213] confirmed that limb development exhibits a segmental pattern; however, recent studies by Streker and Stephens[214] have refuted the proposed role of peripheral nerve damage in thalidomide-induced embryopathy. A foil barrier was placed lateral to the chick neural tube to block the innervation of the wing field by the brachial plexus. A reduced source of innervation from spinal nerves anterior or posterior to the brachial plexus resulted in muscular atrophy but not in reductions or malformations of the wing skeleton. Therefore, the proposals both that the segmental pattern of the limb is determined by level-specific nerves and that diminished levels of innervation will result in skeletal malformations are controversial.

Lash and Saxen postulated that thalidomide indirectly exerts its effects on limb chondrogenesis by acting on the kidney primordia.[215] Based on an association between nephric tissue and limb development,[216,217] Lash and Saxen[215] have in vitro evidence suggesting that thalidomide inhibits an interaction between metanephric tissue and associated mesenchymal tissue necessary for normal limb development.

Thyroid: iodine deficiency, iodides, radioiodine, antithyroid drugs. Iodine deficiency, recently reviewed by Warkany,[218] is the primary cause of endemic cretinism. Damage to the embryo is due to iodine deficiency, occurs early in gestation, and results in irreversible neurologic and aural damage with variable severity. Goiter in a female of reproductive age due to endemic iodine deficiency is an indication for iodine supplementation prior to conception to prevent harmful embryonic effects.

Several drugs used to treat maternal hyperthyroidism (^{131}I and antithyroid drugs) and nonthyroid conditions (especially iodide-containing compounds for bronchitis and asthma) affect thyroid function. In utero exposure to these drugs may result in congenitally hypothyroid infants who will not reach their potential physical or mental development unless treated very early after birth with thyroid hormone.

There are several case reports of congenital goiter due to in utero exposures to iodide-containing drugs.[219,220] Maternal intake of as low as 12 mg per day

may result in fetal goiter.[219] Iodinated contrast agents used for amniofetography have been reported to affect fetal thyroid function adversely.[221] Propylthiouracil and methimazole, used to treat thyrotoxicosis, readily cross the placenta.[225]Methimazole has been associated with aplasia cutis.[222,223] Propylthiouracil is safer because the incidence of fetal goiter is low[224,225] and there have been no observed detrimental effects on mental development.[226,227]

Radioactive iodine, ^{131}I, is a potential risk to the fetal thyroid, especially once the fetal thyroid begins to concentrate iodide at 10 to 12 weeks of gestation. In a retrospective study of fetuses accidentally exposed to ^{131}I during the first or first and second trimesters, six neonates out of 178 live births had hypothyroidism, although other anomalies were statistically increased above the general population.[228] Although there are few case reports in the literature, there is a definite risk of thyroid dysfunction in the offspring. Speert et al.[229] first reported an animal model demonstrating damage to the thyroid of the mouse fetus exposed in utero to ^{131}I after the 15th day of gestation.

TERATOGENIC CONDITIONS ACTING ON HUMANS

Mechanical problems. Although it has been known for a long time that mechanical problems can account for some congenital malformations, it was the late David Smith who revaluated and repopularized this important concept.[230]

Birth defects involving foot position, limb development, skin development, head shape, midline closure defects, ear malformations, and jaw and muscle maldevelopment, all may be produced by mechanical problems of constraint. Pathologic states such as oligohydramnios, uterine malformations (infantile uterus, bifid uterus, uterine myoma), velamentous cord insertion, amniotic bands, umbilical cord bands, extrinsic pressure or uterine contractions could result in distortion and hypoplasia of external structures; failure of closure of the lip, palate, neural tube, and/or abdomen; limb amputation or malposition; or limb reduction defects.

Not only might there be abnormal pressure externally, but these conditions also might interfere with the vascular supply to such superficial structures as the skin, the limbs, or the ears. Substantial experimental work in animals supports these hypotheses for the human.[193]

Maternal starvation. First reported by Smith[231,232] and re-examined by Stein et al.,[233] investigations of the detrimental effects of famine in wartime Holland on the outcome of pregnancy constitute what is probably the most extensive collection of data concerning human intrauterine undernutrition. A famine early in gestation increased prenatal and neonatal mortality, as well as

increasing the incidence of central nervous system abnormalities (spina bifida and hydrocephalus) and prematurity. Exposure to famine late in gestation retarded intrauterine growth. Homeostatic mechanisms in mothers and fetuses appear to minimize variations in fetal growth over a wide range of maternal nutritional states: birth weights were reduced by only about 9% at the peak of the Dutch famine from 1944 to 1945.

Maternal conditions. Maternal conditions such as phenylketonuria[234,235] and diabetes mellitus[236,237] have been associated with an increased incidence of abnormalities: the offspring of mothers with phenylketonuria have a high frequency of mental retardation, microcephaly, and intrauterine growth retardation,[235,238,239] and the offspring of insulin-dependent diabetic mothers have an increased incidence of caudal dysplasia or caudal regression syndrome and of malformations involving multiple organ systems.[237,240]

The introduction of insulin into clinical practice in 1922 made pregnancy possible for many women with diabetes mellitus. Fetal overgrowth was quickly recognized as a complication of the disorder. Pedersen[241] was the first to propose a credible explanation for this fetal overgrowth: maternal hyperglycemia produces fetal hyperglycemia, which in turn stimulates a hypersecretion of insulin by the fetal pancreas. The lipogenic and protein anabolic actions of insulin and glucose result in fetal macrosomia.

Fetal growth retardation observed in 5 to 10% of newborns of diabetic mothers is due most probably to the vascular lesions of long-standing diabetics.

In some situations it may be difficult to determine whether the condition or the treatment for that condition during pregnancy is responsible for malformed infants. In the case of diabetes, however, experimental animal investigations concerning the developmental effects of diabetes have shown that the uncontrolled diabetic condition plays the primary role in congenital defects[242-245] and that insulin therapy can protect the offspring from malformations.[242,243]

Endocrinopathies and endocrine tumors that expose the fetus to excessive hormone concentrations but that do not interfere with the maintenance of pregnancy can be expected to have developmental effects similar to the administration of synthetic hormones, which results in malformations. Thus, it is clinically important that a condition such as pseudohermaphroditism that results from the action of administered hormones can be distinguished from pseudohermaphroditism that results from maternal adrenal tumor or hyperplasia. Although the source of the hormone or the nature (i.e., synthetic versus naturally occurring) of the hormone may vary, a hormone can act only on tissues that contain receptors for that hormone, and not on other tissues.

Infectious agents. Several infectious agents are known to cause maldevelopment in humans. Viral infections include rubella,[246,248] cytomegalovirus,[249] herpes simplex,[250-252] parvovirus B19,[289-293] varicella-zoster,[253] and Venezuelan equine encephalitis.[254,255] Bacterial infections include syphilis,[256,257] and parasitic infections include taxoplasmosis.[258]

Lethal or developmental effects of infectious agents result from mitotic inhibition or direct cytotoxic effects on the embryo or fetus; however, repair processes may result in scarring or calcification, which causes further damage by interfering with histogenesis. It has not been possible to demonstrate dose-response relationships, but transplacental transmission of an infectious agent does not mean necessarily that congenital malformations will result. In the case of some infectious agents not proved teratogenic in humans such as the papovaviruses, the treatment (topical application of podophyllum in this case) has a greater risk of teratognicity than does the infection.[259]

The frequency of embryonic rubella infection after maternal rubella with a rash is more than 80% during the first 12 weeks of pregnancy, 54% at 13 to 14 weeks, 25% at the end of the second trimester, and increased to 100% at term.[260] Defects attributable to rubella result from infections occurring before the 16th week of gestation, however.[260] Rubella causes damage by means of several mechanisms: cell necrosis, obliterative angitis that reduces blood flow to fetal tissues, and release of a mitotic inhibitor from infected cells. The permanent consequences are most probably due to mitotic inhibition, cell death, and interference with histogenesis by repair processes resulting in calcification and scarring.[261]

Cellular necrosis is the principal mechanism by which cytomegalovirus (CMV) damages organs. Six to twenty of every 10,000 infants born in the United States are brain damaged by CMV. If a woman is infected with CMV early in pregnancy, however, the incidence of brain damage in the newborn is approximately 50%. Infections at any time in pregnancy will result in approximately 65% incidence of some eye anomaly, hearing loss, and/or learning disability.

The incidence of fetal herpes virus infections (type 1 or 2) is unknown and is presumed to be very rare. Anomalies include intracranial calcifications, microcephaly, microphthalmia, and retinal dysplasia. Varicella-zoster infections in early pregnancy can cause cell necrosis in widespread fetal tissues, but fetal infection is extremely rare.

Parvovirus B19, discovered in 1975,[289] has been shown to be causal for hydrops fetalis and fetal death.[290,291] Transplacental infection with parvovirus B19 has been demonstrated.[292] Parvovirus B19 selectively infects red blood cell precursors and causes a severe anemia, resulting in congestive

heart failure, edema and fetal death.[293] It appears that infection with parvovirus B19 is not common and that congenital anomalies resulting from parvovirus B19 infection are likely to be a very rare event.[293]

Some infections do not result in congenital malformations but have been shown to cause fetal lesions and death or neonatal death. These include enteroviruses (coxsackievirus, poliovirus, echovirus), hepatitis virus, human immunodeficiency virus, variola, vaccinia, and mumps virus.

Also, asymptomatic newborn infants infected with congenital toxoplasmosis have been shown to progress from mild to severe chorioretinitis and permanent neurologic damage.[262]

The subject of human perinatal infections has been reviewed recently.[259,263]

NONPRESCRIPTION DRUGS AND PRODUCTS

Although drugs and chemicals make a minimal contribution to the overall incidence of malformations, nonprescription medications are of special concern because of our inability to monitor the frequency of use and the dosage used. Table V lists some of the active ingredients contained in a selection of the more common drugs or active ingredients in substances widely used, such as coffee and cigarettes. Of the active ingredients listed, the four substances discussed below are likely to have effects on the developing human or are of current interest.

Aspirin. Animal models of aspirin teratogenesis have shown in rats that increased cell death in the developing preaxial mesoderm is likely to be the cause of aspirin-induced polydactyly.[264] However, data for associations between usual doses of aspirin and congenital malformations in humans are equivocal.[265] Although chronic high exposures can produce low birth weight and a variety of maternal and placental complications that have adverse effects throughout development, there does not appear to be an increased risk of congenital malformations.[266] It is likely that extremely high exposures toxic to the mother would also be embryotoxic.

Caffeine. Caffeine has been reported to have adverse central nervous system effects in experimental animals,[267] but only at high exposures. These and other animal data prompted the Food and Drug Administration to issue a controversial warning concerning caffeine intake during pregnancy.[268] Although available data indicate that caffeine is not a human teratogen,[269-272] chronic excess consumption may have embryotoxic effects.

Smoking and nicotine. Approximately 30% of all women of childbearing age smoke, and about 25% of all women will continue to smoke after they

TABLE V. ACTIVE INGREDIENTS OF SOME NONPRESCRIPTION DRUGS AND PRODUCTS

Amphetamines	Camphor	Sympathomimetics
Antacids	Dextromethorphan	Nicotine
Sodium bicarbonate	Laxatives	Ephedrine
Magnesium trisilicate	Para-aminophenols	Pseudoephedrine
Antihistamines	Acetaminophen	Phenylpropanolamine
Dimenhydrinate	Phenacetin	Vitamins
Diphenhydramine	Acetanalid	A, folic acid, riboflavin,
Chlorpheniramine	Phenols	nicotinamide, B6, B12, C,
Doxylamine	Thymol	D,E,K2,K3
Barbiturates	Hexylresorcinol	Xanthines
Phenobarbital	Salicylate	Caffeine
Belladonna derivatives		Theophylline
Atropine		Theobromine
Scopolamine		

From Schenkel and Vorherr[288]

become pregnant.[273] Human evidence indicates that smoking affects the fetus directly in a dose-related manner and probably involves more than one component of tobacco smoke.[274] Although smoking can retard intrauterine growth, cause a variety of maternal and placental complications, fetal death and increased postnatal morbidity, there is no proved relationship between smoking and specific malformations or malformations in general.[275-277] One study suggests that infants of women who smoked throughout pregnancy experience an increase in mortality, which continues until at least five years of age.[208] Because of the large number of pregnant women who smoke and the documented effects of smoking on the fetus, one may say that smoking is a significant threat to the fetus.

Vitamins. Because the vitamins as a group are essential for normal metabolism, it would seem unlikely that a severe deficiency would be compatible with reproduction and therefore would result in reproductive loss. There is some evidence, however, for an association between folic acid deficiency and increased frequency of neural tube defects.[164,279] Excess prophylactic administration of vitamins is a definite possibility. Excess of vitamins D or A has been associated with increased incidence of congenital malformations. Huge doses of vitamin D administered for rickets prophylaxis markedly increased the incidence of a syndrome consisting of supravalvular aortic stenosis, elfin facies, and mental retardation in humans.[280,281]

There are few case reports of congenital defects in humans associated with massive vitamin A ingestion during pregnancy: two have cited urogenital anomalies,[282,283] and one described Goldenhar's syndrome.[284] Isotretinoin

is a human teratogen that may cause ear malformations, cleft palate, facial abnormalities, and open neural tube, but an association with limb reduction defects[285] is questionable. Vitamin A, especially in the form of retinoic acid, is a potent teratogen in experimental animal models. It appears to have two primary modes of action: direct cytotoxicity and an interaction with DNA that causes a delay in differentiation and/or inhibition of protein synthesis.

PRECONCEPTION EXPOSURES TO NONINFECTIOUS AGENTS

A discussion of the developmental effects of preconception exposures of eggs and sperm to environmental agents is appropriate because of concern raised by some clinicians regarding the teratogenic hazard of such exposures.

A genetic etiology for congenital malformations involves inherited or newly acquired genetic abnormalities that stem from a multitude of possible spontaneous errors or exposures to a mutagenic agent. Thus, a genetic etiology for malformations is not likely for preconception exposure to an environmental teratogen because of the low risk and lack of specificity of mutagens.

Nongenetic preconception effects on the male are not likely to affect the development of offspring for several reasons. Although some infectious agents certainly may be transmitted venereally, drugs or chemicals contained within the ejaculate would be expected to be diluted enough that no increase in malformations could be detected. On the other hand, if the chemical is so potent as still to have cytotoxic effects at extremely low concentrations, it is unlikely that the sperm would survive to fertilize the ovum (since abnormal sperm are not likely to reach the ovum nor to penetrate and fertilize it successfully), nor is it likely that fertilized ova will survive the exposure. If the sperm contains a potentially teratogenic chemical, then the amount of the chemical must be extremely small due to the small volume of the sperm (the head is about 8 μm in diameter and the volume is less than 500 μm^3). Thus, if the sperm fertilizes the ovum (about 120 μm in diameter and about 1.7 million μm^3 in volume), the greater than 3,000-fold dilution of the chemical, due to the large relative volume of the ovum, will reduce the concentration of the chemical to the point at which no increase in malformations could be detected. Finally, any insult to a preimplantation embryo may result in embryonic death or in recuperable damage, but is unlikely to result in congenital malformations.

The oocytes of sexually mature females are arrested at the end of prophase of the first meiotic division. Until the time of ovulation, the oocyte may be exposed to any variety of chemicals and drugs. Although agents may have lethal effects on the oocytes, this ''resting'' stage appears very resistant to the

developmental effects of these agents. Furthermore, a very high proportion of induced mutations are lethal or recessive and therefore will not be manifested in live offspring.

SUMMARY

By far the largest category of malformations, 65% falls into the group of those with an unknown cause(s). Purely genetic causes of malformations (autosomal and cytogenetic), estimated to produce 20 to 25% of all human malformations, comprise the largest group of congenital malformations with known etiology. Although environmental causes of human malformations account for 10% or fewer of malformations, most of these environmentally induced malformations are related to maternal disease states. Fewer than 1% of all human malformations are related to drug exposure, chemicals, or radiation, but studies of environmentally induced malformations are important because they may teach us how to predict and test for teratogenicity, understand the mechanisms of teratogenesis from all etiolgies, and provide a means by which human malformations can be prevented.

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